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REVIEW

Diagnostic and Therapeutic Challenges for Patients with Idiopathic Pulmonary Fibrosis and Lung Cancer

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic, debilitating lung disease with a steady increase in both incidence and mortality. Patients with IPF present with an increased risk for lung cancer development compared to the general population, while lung cancer development has a major impact on patients' prognosis. Importantly, lung cancer development has an increased risk during the IPF course. Nonetheless, well-designed prospective studies for patients with IPF and lung cancer are currently lacking. Thus, there seems to be major heterogeneity in diagnostic and therapeutic strategies for these patients. This review article aims to address the main diagnostic and therapeutic challenges for patients with IPF and lung cancer. **(BRN Rev. 2021;7(2):115-24)**

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) represents a chronic, debilitating lung disease of unknown origin and pathogenesis with a steady increase in both incidence and mortality[1]. Despite the advent of anti-fibrotics, these compounds manage only to slow down disease progression and thus IPF still remains the non-cancer lung disease with the gravest prognosis[2]. The prognosis of patients with IPF is dramatically affected by the underlying comorbidome such as lung cancer[2,3]. Epidemiological evidence suggests that patients with IPF have a fivefold higher risk for lung cancer development compared to the general population. The reported prevalence of lung cancer in patients with IPF ranges from 2.7% to 31.3% with an increased risk during disease course up to 50%[2,4-6].

IPF and lung cancer share striking pathogenetic commonalities such as telomere attrition, microsatellite instability, epigenetic alterations and impaired cellular bioenergetics[2,7-10]. In line with these, nintedanib, a triple kinase inhibitor, initially launched as an anti-cancer compound, was successfully repurposed for patients with IPF [9,11-17]. Despite major advances, there is still a lack of high-quality prospective studies evaluating therapeutic interventions including antifibrotics in patients with IPF and concomitant lung cancer[2].

To this end, there is still a considerable lack of agreement on the diagnostic and therapeutic management of these patients[18]. Current American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and Latin American Thoracic Society (ALAT) guidelines do not address this crucial issue[1,7]. A recently published international survey, denominated the DIAMORFOSIS (DIAgnosis and Management Of lung canceR and FibrOSIS) survey, identified major heterogeneity in diagnostic and management strategies across different institutions and highlighted the amenable need for a consensus statement[19]. This review article aims to address the main diagnostic and therapeutic challenges for patients with IPF and lung cancer through a Q (questions) and A (answers) approach.

IS LUNG CANCER PREVALENT IN PATIENTS WITH IPF?

IPF represents a risk factor for lung cancer development[12,13,16,17]. Epidemiological evidence suggests a fivefold higher risk for lung cancer development in patients with IPF compared to the general population. Prevalence of lung cancer in patients with IPF has been reportedly ranging from 2.7% to 31.3% (Table 1)[4,5,16,17,20-27]. Most large multicenter studies, including the recently published study from Greece enrolling 1016 patients with IPF, showed lung cancer development in around 10% of patients with IPF[6]. However, the cumulative incidence seems to increase during the disease course and may even exceed 50% at 10 years of follow-up[4,5,28]. Therefore, the prevalence and incidence of lung cancer in the era of antifibrotics remains an open question. On the one hand, it seems plausible that survival prolongation will increase dramatically the risk for lung cancer development. On the other hand, recent reports have suggested that pirfenidone might reduce lung

Table 1. Main studies reporting prevalence of lung cancer in patients with IPF

Study	Number of patients with IPF	Prevalence of lung cancer	Year	Reference
Nagai	99	31 (31.3%)	1992	21
Park	281	63 (22.4%)	2001	24
Le Jeune	1064	29 (2.7%)	2007	20
Ozawa	103	21 (20.4%)	2009	4
Kreuter	265	42 (16%)	2014	33
Tomassetti	181	23 (13%)	2015	5
Kato	632	70 (11.1%)	2018	23
Tzouvelekis	1016	102 (10%)	2020	6

IPF: Idiopathic pulmonary fibrosis.

cancer prevalence, while nintedanib was initially launched as an anticancer compound[29-32].

WHICH IS THE MOST COMMON HISTOLOGIC TYPE OF LUNG CANCER IN PATIENTS WITH IPF?

Squamous cell carcinoma is the most frequent histologic type of lung cancer in patients with IPF (30-46% of total cases), while the prevalence of adenocarcinoma is slightly lower (Table 2)[4-6,24-26,28,33]. In contrast, adenocarcinoma is the most common histologic type in the general population. Intriguingly, patients with IPF develop more frequently tumors in the lung periphery of the lower lobes and this phenomenon has been denominated ''scar-cinoma''; despite the fact that adenocarcinoma is more common in lung periphery in the general population, it might not be that prevalent in this subpopulation[2,12,34].

WHICH ARE THE MAIN DIAGNOSTIC CHALLENGES FOR PATIENTS WITH IPF AND LUNG CANCER?

The latest US Preventive Services Task Force Recommendation Statement recommended that all patients with IPF should be considered as high-risk for lung cancer development[4]. Close monitoring by means of annual high-resolution computed tomography (HRCT) should be considered as the minimum mandatory radiologic follow-up, similarly with other chronic lung diseases such as COPD[35]. Nonetheless, in specific cases, radiologic follow-up might be even more frequent. The benefit from the aforementioned close follow-up remains to be shown in high-quality prospective studies of patients with IPF, as it has been shown in middle-aged smokers.

Meticulous evaluation for the development of nodular lesions in areas of pulmonary fibrosis or areas adjacent to vessels is sorely needed for early diagnosis (Fig. 1). Optimal

Table 2. Main studies reporting most common histologic types of lung cancer in patients with IPF

Study	Number of patients with IPF-lung cancer	SQLC	ADC	Year	Reference
Nagai	31	45.2%	35.2%	1992	21
Park	63	35%	30%	2001	24
Kawasaki	53	46%	46%	2001	25
Ozawa	21	38%	29%	2009	4
Lee	70	40%	30%	2014	26
Kreuter	42	36%	31%	2014	33
Tomassetti	23	39%	35%	2015	5
Kato	70	30%	20%	2018	23
Tzouvelekis	102	34.3%	27.5%	2020	6

ADC: adenocarcinoma; IPF: idiopathic pulmonary fibrosis, SQLC: squamous cell lung cancer.

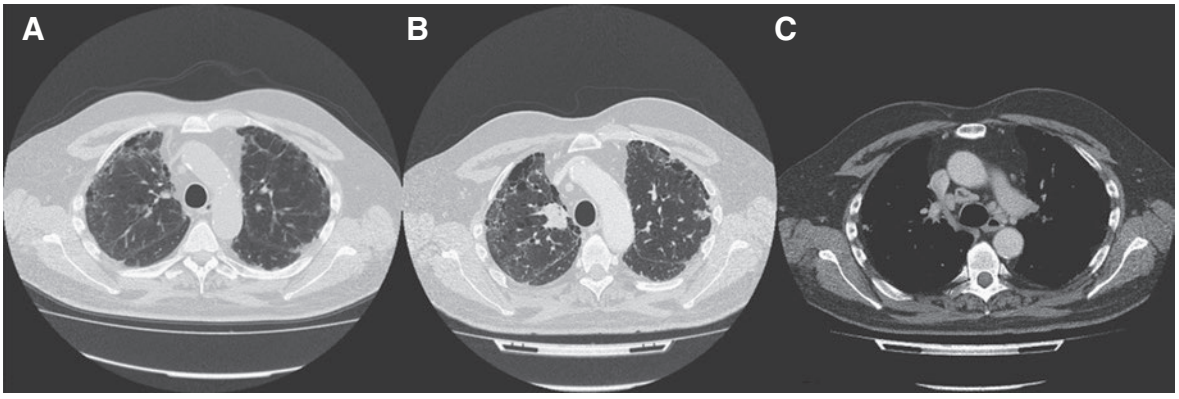

Figure 1. HRCT of a 77-year old patient with IPF, showing a perihilar nodular lesion in the right upper lobe (**A**). Nine months later, the patient presented for the first time in our department with a second HRCT showing a mass in the right upper lobe as well as mediastinal lymphadenopathy (**B**, **C**). EBUS guided biopsy of the mass, right lower paratracheal and subcarinal lymph nodes demonstrated squamous cell carcinoma.
EBUS: endobronchial ultrasound; HRCT: high-resolution computed tomography; IPF: Idiopathic pulmonary fibrosis.

selection for diagnostic interventions of patients with IPF and highly suspicious for malignancy nodular lesions remains a matter of ongoing debate. In the recently published DIAMORFOSIS survey, participants agreed that patients with mild-to-moderate IPF and otherwise operable lung cancer should be thoroughly investigated with positron emission tomography (PET) and endobronchial ultrasound-guided transbronchial needle

aspiration/biopsy (EBUS-TBNA/B)[19]. On the contrary, agreement rates were considerably decreased in cases of severe IPF[19]. However, EBUS-TBNA/B in centers of expertise seems to be a safe procedure and maybe even safer than bronchoalveolar lavage[36,37]. Thus, patients with acceptable performance status might experience benefit from timely diagnostic interventions. Prospective studies are greatly anticipated to prove these concepts.

HOW SHOULD WE TREAT A PATIENT WITH MILD-TO-MODERATE IPF AND OTHERWISE OPERABLE NON-SMALL CELL LUNG CANCER? ARE THERE ANY SAFETY PRECAUTIONS FOR PATIENTS WITH IPF AND NON-SMALL CELL LUNG CANCER UNDERGOING SURGICAL LUNG INTERVENTIONS?

Retrospective studies have demonstrated that patients with IPF exhibit increased risk for postoperative acute respiratory events[5,38-41], especially acute exacerbation[42,43]. A large retrospective Japanese cohort enrolling 1763 patients with different forms of interstitial lung diseases (ILDs) undergoing lung resection for lung cancer showed that duration and extent of surgical procedures, peri-operative fraction of inspired oxygen and fluid intake were independent risk factors of acute exacerbations[44]. A retrospective study of 350 patients with pathologic stage IA non-small cell lung cancer undergoing pulmonary resection demonstrated significantly reduced five-year survival rate in patients with non-small cell lung cancer and concomitant IPF compared to patients without IPF (54.2% versus 88.3%)[45]. Accordingly, a study enrolling 870 patients with surgically treated primary lung cancer reported higher surgery-related mortality (7.1 % versus 1.9%) and lower five-year survival lower (61.6% versus 83.0%) for patients with IPF[46].

Based on the above, surgical lung interventions should be performed in highly selected cases based on reliable prognosticators such as functional indices, composite physiologic index, history of exacerbations, Krebs von den Lungen-6 (KL-6) and lactate dehydrogenase (LDH) (Fig. 2)[44,47-54]. A preoperative multi-disciplinary evaluation should be conducted and include thoracic surgeons, as well as anesthesiologists, so as to increase awareness and monitoring on peri- and post-operative complications of non-protective lung ventilation and excessive tissue manipulation in patients with severely impaired lung compliance, such as patients with IPF[55]. Expert opinion suggests that reduction of the duration of one-lung ventilation, low-tidal volume ventilation strategies, avoidance of high fraction of inspired oxygen, videothoracoscopic surgery under spontaneous ventilation in selected patients, and minimal tissue manipulation perioperatively may exert prophylactic effects[56,57].

IS IRRADIATION TREATMENT BENEFICIAL OR DETRIMENTAL?

Scarce data has shown detrimental effects of irradiation treatment on patients with pulmonary fibrosis[33], as there is an increased risk for radiation pneumonitis and pneumothorax[58]. This is of paramount importance especially for patients with Combined Pulmonary Fibrosis and Emphysema (CPFE)[59]. Interestingly, despite

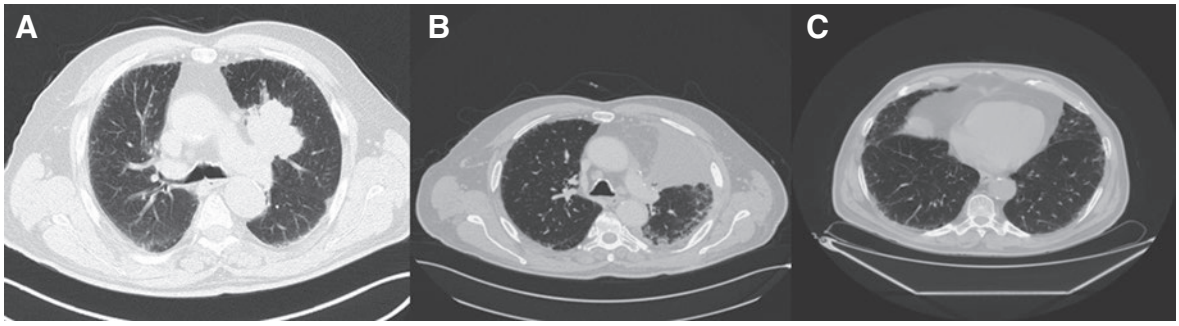

Figure 2. Concomitant diagnosis of IPF and squamous cell lung cancer (**A**). EBUS-TBNB was performed. Mediastinal and hilar lymph nodes were negative for malignancy and thus the patient underwent left upper lobe lobectomy, given his acceptable functional status. Surgical resection of the mass was successful without significant adverse events (**B**, **C**).
EBUS-TBNB: endobronchial ultrasound-guided transbronchial needle aspiration; IPF: Idiopathic pulmonary fibrosis.

the aforementioned data, stereotactic radiotherapy was the predominant therapeutic intervention among clinicians for patients with severe IPF and otherwise operable lung cancer in the recently published DIAMORFOSIS survey[19]. Finally, proton beam therapy has recently shown promising results with regards to safety in a small, retrospective study of patients with IPF and lung cancer[60]. Our personal view is that radiotherapy should be generally avoided unless life-threatening situations arise (Fig. 3).

SHOULD CHEMOTHERAPY BE APPLIED IN PATIENTS WITH IPF AND LUNG CANCER?

High-quality randomized trials for the optimal chemotherapeutic regimen in patients with IPF and lung cancer are currently lacking. Results from docetaxel monotherapy and docetaxel-containing regimens were discouraging with low overall response rates[61,62]. Pulmonary toxicity was higher in patients with ILD treated with either docetaxel, pemetrexed and etoposide-based regimens[61,63]. In particular, patients with interstitial pneumonia (UIP) presented with increased risk for pulmonary toxicity due to pemetrexed (16.7%) compared to patients without ILD (3.5%) or patients with non-IPF-ILD (12.0%)[64]. To this end, only carboplatin has been associated with moderate therapeutic effects and minimal toxicity[65]. A randomized controlled study (J-SONIC) investigating the efficacy of carboplatin plus nab-paclitaxel with or without nintedanib in patients with advanced non-small cell lung cancer and IPF is ongoing in Japan. Studies investigating the safety and efficacy of novel immunomodulatory compounds such as programmed death-ligand (PD-L) 1 inhibitors would be of paramount importance for a selective number of cases especially those with deregulated PD-1/PD-L1 axis[8,66]; nonetheless,

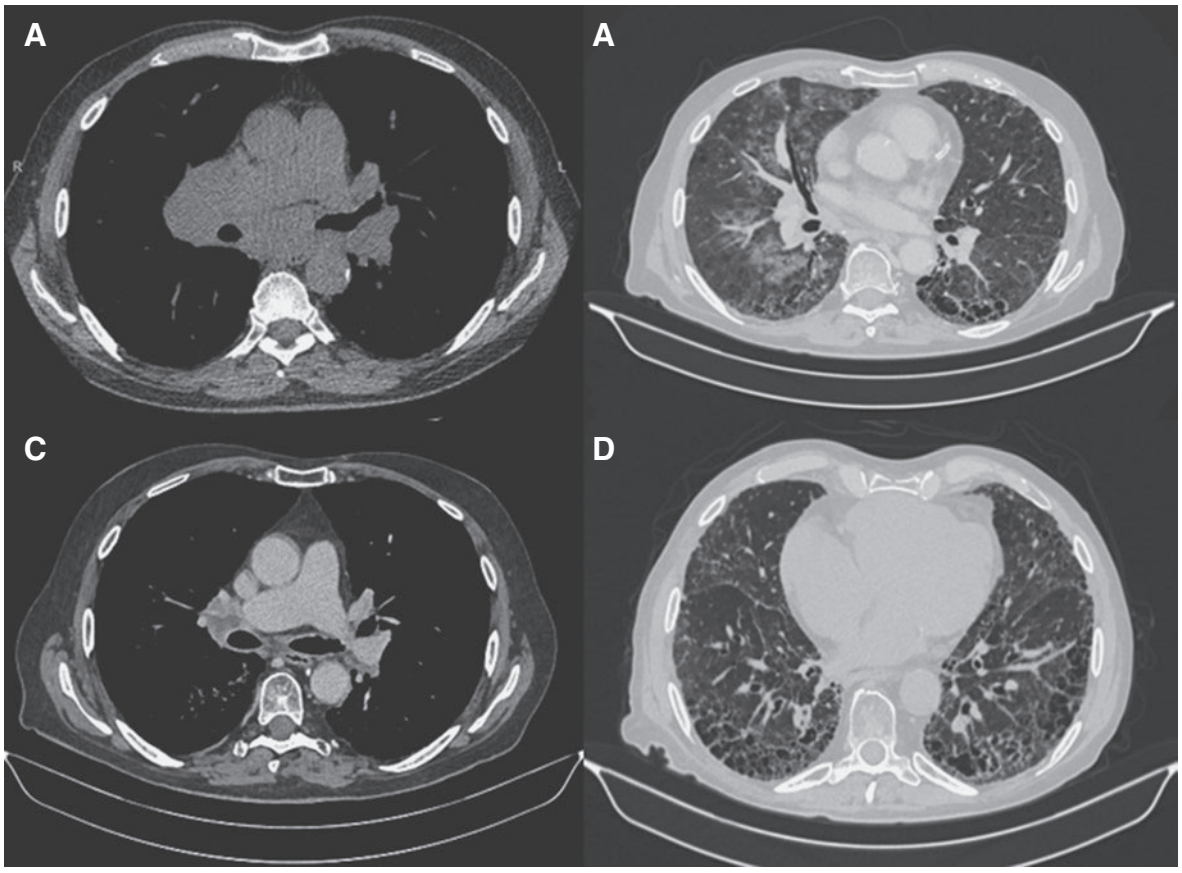

Figure 3. HRCT of a 66-year old male, ex-smoker, indicative of CPFE, as well as mediastinal lymphadenopathy (**A**, **D**). Following MDD, stereotactic radiotherapy was applied; however, the patient developed irradiation-induced pneumonitis, as indicated by newly formed ground glass and consolidative opacities (**B**). Clinical and radiologic improvement was shown following short course of oral corticosteroids. Importantly, substantial reduction of mediastinal lymph nodes size was noticed following concomitant stereotactic radiotherapy and chemotherapy with platinum-doublets (**A**, **C**).
CPFE: combined pulmonary fibrosis and emphysema; HRCT: high-resolution computed tomography; MDD: multidisciplinary discussion.

caution is demanded due to the risk of ILD associated with PD-1 and PD-L1 inhibitors[67-69].

SHOULD WE CONTINUE ANTI-FIBROTIC TREATMENT?

Another challenge of the real-life clinical practice is whether anti-fibrotic compounds could be combined or even synergize with chemotherapeutic agents. Nintedanib has been initially approved as a second-line therapy in combination with docetaxel for the treatment of non-squamous, non-small-cell lung cancer[70]. Given the antiangiogenic properties of nintedanib, future studies should address the safety of nintedanib during the pre- and peri-operative period of patients with IPF and lung

cancer. Retrospective data suggested a beneficial effect of preoperative pirfenidone on the incidence of postoperative acute exacerbations in patients with adenocarcinoma and IPF[30,32,71]. To this end, the majority of clinicians continue anti-fibrotics in patients with IPF and lung cancer based on the results of DIAMORFOSIS survey, as benefits seem to outweigh the risk of adverse outcomes[19]. The role of nintedanib monotherapy as an anti-cancer regimen in patients with IPF and lung cancer needs to be addressed in the context of clinical trials.

WHAT STANDS FOR THE FUTURE?

Well-designed, large, prospective studies using validated outcome measures are sorely needed so as to assess interventional methods, chemotherapeutic regimens, irradiation, anti-fibrotics and palliative care on symptoms, quality of life and survival of patients with IPF and lung cancer irrespective of disease severity[72-74]. Identification of reliable prognostic indicators of treatment responsiveness and application of pharmacogenomics should be aggressively pursued[75]. Further data of molecular testing for PD-L1, epidermal growth factor-receptor (EGFR), anaplastic lymphoma kinase (ALK) and Kirsten rat sarcoma viral oncogene homolog (KRAS) profile of these patients are greatly anticipated. Identification of pathogenetic commonalities between IPF and lung cancer could lead to further available compounds through drug positioning as it happened with nintedanib[76,77]. Until novel studies shed light on diagnostic and therapeutic modalities, timely identification of suspicious-for-malignancy-nodes and mediastinal lymphadenopathy might be crucial[78].

To this end, the lack of well-designed studies and the uncertainty in key areas of the field seem to lead to major heterogeneity in diagnostic and therapeutic strategies for patients with IPF and lung cancer. A consensus statement is greatly anticipated for harmonized and standardized management approaches with a beneficial impact on patients' survival.

DISCLOSURES

Dr. Karampitsakos, Dr. Bouros, and Dr. Tzouvelekis have nothing to disclose.

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